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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HENRY, MICHAEL C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,329	BISSERY, MARIE CHRISTINE	
	Examiner	Art Unit	
	Michael C. Henry	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The following office action is a responsive to the RCE filed, 09/01/05.

The amendment filed 07/27/04 affects the application, 09/809,329 as follows:

1. New claims 21-27 have been added. This leaves claims 13-27.

The responsive to applicants' arguments is contained herein below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuta et al. (Jpn J Cancer Chemother 18 (3): 393-402, 1991).

In claim 13, applicant claims a method of treating a solid tumor, comprising administering an effective amount of camptothecin, or a camptothecin derivative, as a first agent, in combination with an effective amount of a topoisomerase II inhibitor as a second agent, wherein the agents are administered simultaneously, semi-simultaneously, or separately, and wherein said first and second agents provide a therapeutic synergy superior to each of the agents used alone at its optimum dose in the treatment of said solid tumor. Dependent claims 14-19 are drawn to methods involving specific camptothecin derivatives (teniposide and etoposide) and specific topoisomerase II inhibitors (adriamycin (doxorubicin) and daunomycin (daunorubicin)). It should be noted that claims 14-19 are also obvious in view of Furuta et al., since Furuta et al. also use the same antitumor agents (adriamycin and etoposide) or antitumor agents that belong to

the same genus as (daunomycin) and (teniposide). Dependent claim 20 is drawn to the method according to any one of claims 13-19, wherein the camptothecin derivative is administered orally. Dependent claims 21-27 are drawn to said method involving specific first agent, specific anthracycline antibiotics, specific solid tumors and specific routes of administration agents.

Furuta et al. disclose a method of treating a tumor (L 1210 leukemia), comprising administering an effective amount of a camptothecin derivative, as a first agent, in combination with administration of an effective amount of a topoisomerase II inhibitor as a second agent, wherein the agents are administered simultaneously, semi-simultaneously, or separately and wherein said first and second agents provide a synergistic effect (see abstract and tables).

The difference between applicant's claimed method and the method taught by Furuta et al. is the type of tumor that is treated, the form of administration of said agents and the fact that Furuta et al. is silent about whether or not the dose of their agents is an optimum dose. However, Furuta et al.'s dose may well be an optimum dose since such dose is not defined in terms of a tangible quantity, amount or concentration. Also, if Furuta et al.'s dose is not an optimum dose then Furuta et al.'s dose produces the same synergy (i.e. therapeutic synergy) at a dose that is less than optimum dose. Furthermore, it is obvious and common in the art to optimize the doses of such drug or agent combinations in the treatment of tumors.

It would have been obvious to one having ordinary skill in this art, at the time the claimed invention was made, in view of Furuta et al., to use the method of Furuta et al. to treat various types of tumors like solid tumors, and to use antitumor agents taught by Furuta et al. that belong to the same genus as (adriamycin and daunomycin) and (teniposide and etoposide) for the treatment of different tumors using any common administrative form (e.g. oral administration)

and any dose (e.g optimum dose), based on need, like the type and/or degree of severity of the tumor and the subject that is treated.

One having ordinary skill in the art would have been motivated in view of Furuta et al., to use the method of Furuta et al. to treat various types of tumors like solid tumors, and to use antitumor agents taught by Furuta et al. that belong to the same genus as (adriamycin and daunomycin) and (teniposide and etoposide) for the treatment of different tumors using any common administrative form (e.g. oral administration) and any dose (e.g optimum dose), based on need, like the type and/or degree of severity of the tumor and the subject that is treated. It should be noted that merely modifying the process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. In re Aller; 220 F.2d 454, 105 U.S.P.Q. 233 (C.C.P.A. 1955).

Response to Amendment

Applicant's arguments filed September 9, 2005 have been fully considered but they are not persuasive.

The applicant argues that the teachings in Furata et al. are limited to the treatment of L1210 leukemia, which, as one skilled in the art knows, is not a solid tumor. There is no teaching or suggestion therein that this combination would be useful for treating solid tumors, as claimed herein. However, applicant claims the treatment of solid tumors which includes or encompasses several types of tumors such as sarcomas, carcinomas and lymphomas. It is commonly known in the art that some therapeutic agents are effective against both solid and leukemias. Moreover, camptothecin and topoisomerase II inhibitors are known to be used in the treatment of both solid tumors and leukemia. Thus, one would be motivated to use Furata et al.'s combination to treat

solid tumors in addition to leukemia. For example, Lackey et al. in US 5,342,947 patent disclose that camptothecin's cytotoxic activity is thought to be directly related to camptothecin's potency as a topoisomerase inhibitor. [For detailed explanations of the topoisomerase function see A. Lehninger, Principles of Biochemistry, 813, Worth Publishers, New York (1982); L. F. Liu, "DNA Topoisomerases," CRC Critical Review in Biochemistry, 1-24, 15 (1983) and H Vosberg, "DNA Topoisomerases: Enzymes that Control DNA Conformation," Current Topics in Microbiology and Immunology, 19, Springer-Verlag, Berlin (1985).] In particular, camptothecin has been shown to be effective in the treatment of leukemia (L-1210) and certain solid tumors in laboratory animals, e.g., see Chem. Rev. 23, 385 (1973) and Cancer Treat. Rep., 60, 1007 (1967) (see US 5,342,947, col.1, lines 35-50). Furthermore, US 5,786,344 patent discloses that the campthothecin analogues (derivatives) have well-documented activity against resistant solid tumors particularly colon, lung cancer and ovarian cancer, and refractory leukemia. CPT-11 itself has shown antitumor activity in phase II trials in patients with carcinomas of lung, cervix, ovary, colon, and rectum and in patients with non-Hodgkin's lymphoma. However, it will be appreciated that the camptothecins may be used to treat practically any cancer (see US 5,786,344, col. 9, lines 58-67 to col. 10, line 2). In addition, US 5,646,159 discloses camptothecin compounds (derivatives) that are effective in treating in treating leukemia and solid tumors in mammals and humans (see US 5,646,159, col. 7, lines 22-37). Also, Felix et al. (Blood (1996), 87 (10), 4376-4381) disclose that primary cancers including solid tumors and leukemias can be treated with topoisomerase II inhibitors (see abstract). Furthermore, Kushner et al. (Journal of Clinical Oncology, (1998 Sep) 16 (9) 3016-20) disclose that topoisomerase II inhibitors can be used to treat patients with solid tumors. The applicant argues that Furata et al.

did not evaluate the effect of the highest non-toxic dose of campotothecin or doxorubicin when administered as a single agent. Without such a determination it is not possible to determine the synergestic effect of the CPT-I 1 and doxorubicin combination or whether there is any "therapeutic synergy" described therein, as that term is defined in the claims. However, synergism or therapeutic synergy is not limited to an optimum dose (i.e., highest non-toxic dose) and therefore, Furuta et al. do not have to disclose an optimum dose (i.e., highest non-toxic dose) in reporting synergism or synergistic effects of their composition. Also, Furuta et al. data of Table 3 shows that the effect (survival times) of two chemicals (CPT-II and adriamycin) on the inoculated mice (an organism) is greater than the effect of each of these chemicals individually (for example, 12.5 mg/kg of CPT-II + 6.25 mg/kg of adriamycin produces a survival time of 16.5 ± 1.7 days whereas, 12.5 mg/kg of CPT-II produces a survival time of 10.8 ± 0.4 days and 6.25 mg/kg of adriamycin or doxorubicin produces a survival time of 11.7 ± 0.7 days; based on three administrations (days 1,5,9) per dosing regimen). This result complies with the latter stated definition of synergism or synergistic effect and also with applicant's definition excluding the limitation or term, "when used at maximum dose". In addition, applicant argues that the Examiner's statement pertaining to the data in table 3, is not supported by all, and is contrary to some, of the data in Furuta. However, the aforementioned results of Furuta et al. are the results of a single experiment at the given concentrations and a comparison to other results from other experiments (as presented or argued by applicant) is irrelevant, especially since other experiments involve different conditions. Furthermore, applicant argues that the rate of survival for mice treated with the therapeutic synergistic combination is almost double the rate of survival for the mice treated with the individual constituents alone, and more than three times the rate

reported in Furuta. However, in the absence of a side-by-side comparison between applicant's composition and Furuta et al. composition (which involves the same specific conditions and experimental parameters) one cannot assume that Furuta et al. composition would not give the same results. As applicant indicated, the data in Table IV (i.e., applicant's data) is not directed to days of survival as in Furuta, but instead, it is directed to the time in days for the tumors to reach 1000 mg. This difference in measured parameters or conditions is one example that indicates the absence of the said side-by-side comparison. Moreover, applicant's therapeutic synergistic pharmaceutical composition, as claimed reads on Furuta et al.'s composition, since Furuta et al. composition contains the same ingredients or components as applicant's composition. It should be noted that applicant does not claim any specific amounts, quantities or concentrations of the said composition or components of the composition that equates to a maximum or optimum dose, or that renders his/her composition different from Furuta et al.'s composition. Thus, Furuta et al's composition is the same as applicant's claimed composition and should have the same therapeutic synergistic effect when administered under the same conditions. In addition, it should also be noted that merely modifying the process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. In re Aller, 220 F.2d 454, 105 U.S.P.Q. 233 (C.C.P.A. 1955).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8:30 am to 5:00 pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be

reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-1235.

MCH

November 23, 2005.

SAMUEL BARTS
PRIMARY EXAMINER
GROUP 1600